

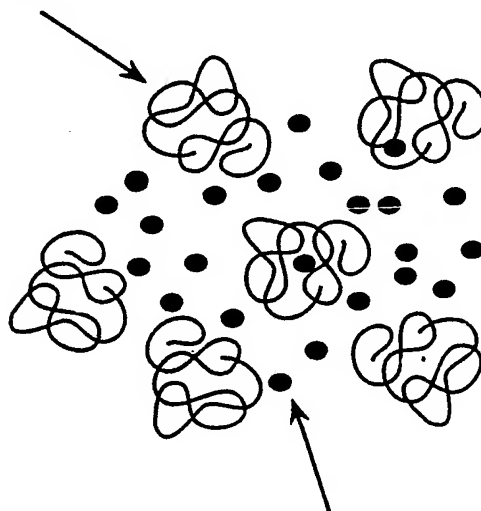


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(54) Title: POLYMERS AS CONTRAST MEDIA FOR MAGNETIC RESONANCE IMAGING

Polymer



Contrast Agent

(57) Abstract

Novel contrast media for use in magnetic resonance imaging are described. Such contrast agents are comprised of biocompatible polymers either alone or in admixture with one or more contrast agents such as paramagnetic, superparamagnetic or proton density contrast agents. Additionally, the polymers or polymer and contrast agent admixtures may be mixed with one or more biocompatible gases to increase the relaxivity of the resultant preparation.

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- 1 -

**Polymers as Contrast Media
for Magnetic Resonance Imaging**

BACKGROUND OF THE INVENTION

Field of the Invention

5 This invention relates to the field of magnetic resonance imaging, more specifically to the use of polymers or polymers in combination with contrast agents and/or gases as contrast media for magnetic resonance imaging.

Description of the Prior Art

10 There are a variety of imaging techniques that have been used to diagnose disease in humans. One of the first imaging techniques employed was X-rays. In X-rays, the images produced of the patients' body reflect the different densities of body structures. To improve the diagnostic utility of this
15 imaging technique, contrast agents are employed to increase the density between various structures, such as between the gastrointestinal tract and its surrounding tissues. Barium and iodinated contrast media, for example, are used extensively for X-ray gastrointestinal studies to visualize
20 the esophagus, stomach, intestines and rectum. Likewise, these contrast agents are used for X-ray computed tomographic studies to improve visualization of the gastrointestinal tract and to provide, for example, a contrast between the tract and the structures adjacent to it, such as the vessels or lymph
25 nodes. Such gastrointestinal contrast agents permit one to increase the density inside the esophagus, stomach, intestines

- 2 -

and rectum, and allow differentiation of the gastrointestinal system from surrounding structures.

Magnetic resonance imaging (MRI) is a relatively new imaging technique which, unlike X-rays, does not utilize ionizing radiation. Like computed tomography, MRI can make cross-sectional images of the body, however MRI has the additional advantage of being able to make images in any scan plane (i.e., axial, coronal, sagittal or orthogonal). Unfortunately, the full utility of MRI as a diagnostic modality for the body, particularly in the abdominal and pelvic region, is hampered by the lack of an effective gastrointestinal contrast agent. Without such an agent, it is often difficult using MRI to differentiate the intestines from, for example, adjacent soft tissues and lymph nodes. If better contrast agents were available, the overall usefulness of MRI as an imaging agent would improve, and the diagnostic accuracy of this modality in the gastrointestinal region would be greatly enhanced.

MRI employs a magnetic field, radiofrequency energy and magnetic field gradients to make images of the body. The contrast or signal intensity differences between tissues mainly reflect the T1 and T2 relaxation values and the proton density (effectively, the free water content) of the tissues. In changing the signal intensity in a region of a patient by the use of a contrast medium, several possible approaches are available. For example, a contrast medium could be designed to change either the T1, the T2 or the proton density.

A paramagnetic contrast agent such as Gd-DTPA causes longitudinal relaxation to shorten T1. This increases the signal intensity on T1-weighted images. A superparamagnetic contrast agent such as ferrites works predominantly on transverse relaxation causing a shortening of T2 and decreasing signal intensity on T2-weighted images. A contrast agent could also work by altering the proton density, specifically by decreasing the amount of free water available that gives rise to the signal intensity.

Agents that increase the signal intensity from the

- 3 -

lumen compared to the native contents are termed positive contrast agents. A number of these have been examined as contrast agents for MRI. These include fats and oils (Newhouse et al., Radiology, 142(P):246 (1982)), which
5 increase signal as a result of their short T1, long T2 and high intrinsic proton density, as well as various paramagnetic agents that increase signal by decreasing the T1 of water protons. Examples of such paramagnetic agents include Gd-DTPA (Kornmesser et al., Magn. Reson. Imaging, 6:124 (1988), and
10 Laniado et al., AJR, 150:817 (1988)), Gd-DOTA (Hahn et al., Magn. Reson. Imaging, 6:78 (1988)), Gd-oxalate (Runge, V.M. et al., Radiology, 147:789 (1983)), Cr-EDTA (Runge, V.M. et al., Physiol. Chem. Phys. Med. NMR, 16:113 (1984)), Cr-Tris-acetylacetonate (Clanton et al., Radiology, 149:238 (1983)),
15 ferric chloride (Young et al., CT, 5:543 (1981)), ferrous gluconate (Clanton et al., Radiology, 153:159 (1984)), ferric ammonium citrate and ferrous sulfate (Wesbey et al., Radiology, 149:175 (1983) and Tscholakoff et al., AJR, 148:703 (1987)) as well as iron complexes (Wesbey et al., Magn. Reson.
20 Imaging, 3:57 (1985) and Williams et al., Radiology, 161:315 (1986)).

Alternatively, agents that decrease the signal intensity from the lumen are termed negative contrast agents. Examples include particulate iron oxides (Hahn et al.,
25 Radiology, 164:37 (1987), Widder et al., AJR, 149:839 (1987)) which decrease signal via T2 shortening, as well as gas-evolving materials (Weinreb et al., J. Comput. Assist. Tomogr., 8:835 (1984)) and perfluorocarbons (Mattrey et al., AJR, 148:1259 (1987)) which act through changes in the proton
30 density. It should be recognized that all paramagnetic substances at sufficiently high concentrations can also result in a decrease in signal intensity via T2 shortening.

The existing MRI contrast agents all suffer from a number of limitations when employed as oral gastrointestinal
35 agents. Positive contrast agents increase the image noise arising from intrinsic peristaltic motions and motions imposed via respiration or cardiovascular action. Positive

- 4 -

contrast agents such as Gd-DTPA are subject to the further complication that the signal intensity depends upon the concentration of the agent as well as the pulse sequence used. Absorption of contrast agent from the gastrointestinal tract complicates interpretation of the images, particularly in the distal portion of the small intestine, unless sufficiently high concentrations of the paramagnetic species are used (Kornmesser et al., Magn. Reson. Imaging, 6:124 (1988)). Negative contrast agents by comparison are less sensitive to variation in pulse sequence and provide more consistent contrast. However at high concentrations, particulates such as ferrites can cause magnetic susceptibility artifacts which are particularly evident in the colon where the absorption of intestinal fluid occurs and the superparamagnetic material may be concentrated. Negative contrast agents typically exhibit superior contrast to fat, however on T1-weighted images, positive contrast agents exhibit superior contrast versus normal tissue. Since most pathological tissues exhibit longer T1 and T2 than normal tissue, they will appear dark on T1-weighted and bright on T2-weighted images. This would indicate that an ideal contrast agent should appear bright on T1-weighted images and dark on T2-weighted images. None of the currently available MRI contrast media for use with the gastrointestinal tract meet these dual criteria.

Toxicity is another problem with the existing contrast agents. With any drug there is some toxicity, the toxicity generally being dose related. With the ferrites there are often symptoms of nausea after oral administration, as well as flatulence and a transient rise in serum iron. The paramagnetic contrast agent Gd-DTPA is an organometallic complex of gadolinium coupled with the complexing agent diethylene triamine pentaacetic acid. Without coupling, the free gadolinium ion is highly toxic. The peculiarities of the gastrointestinal tract, wherein the stomach secretes acids and the intestines release alkalines, raise the possibility of decoupling and separation of the free gadolinium from the complex as a result of these changes in pH during

- 5 -

gastrointestinal use. Certainly, minimizing the dose of either gastrointestinal contrast agent, whether paramagnetic or superparamagnetic, is important for minimizing any potential toxic effects.

5 New and/or better contrast agents useful in magnetic resonance imaging, particularly in the imaging of the gastrointestinal tract but also in the imaging of other regions of the body such as through the vasculature, are needed. The present invention is directed to this important
10 end.

SUMMARY OF THE INVENTION

The present invention is directed to a contrast medium useful for magnetic resonance imaging, said contrast medium comprising an aqueous solution of at least one
15 biocompatible polymer. Optionally, the contrast medium further comprises, in admixture, contrast agents, especially paramagnetic, superparamagnetic and/or proton density contrast agents. The polymer or polymer and contrast agent admixtures may also comprise, if desired, biocompatible gases, preferably
20 gases such as air, oxygen, carbon dioxide, nitrogen, xenon, neon and/or argon.

The subject invention also pertains to a method of providing an image of an internal region of a patient, especially an image of the gastrointestinal region of the
25 patient, said method comprising (i) administering to the patient one or more of the aforementioned contrast agents, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images of the region.

Finally, the present invention encompasses a method
30 for diagnosing the presence of diseased tissue in a patient, especially in the gastrointestinal region of the patient, said method comprising (i) administering to the patient one or more of the foregoing contrast agents, and (ii) scanning the patient using magnetic resonance imaging to obtain visible
35 images of any diseased tissue in the region.

These and other aspects of the invention will become

- 6 -

more apparent from the following detailed description when taken in conjunction with the following drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a diagrammatic view of a contrast
5 medium in accordance with the present invention;

Fig. 2 is a graph of relaxation rate (1/sec)
versus percent polyethylene glycol (w/w), wherein the
polyethylene glycol polymer is in aqueous solution both
with and without a Gd-DTPA contrast agent;

10 Fig. 3 is a graph of relaxation rate (1/sec)
versus percent dextrose (w/w), wherein the dextrose polymer
is in aqueous solution both with and without a Gd-DTPA
contrast agent;

Fig. 4 is a graph of $1/T_2$ (1/sec) versus ferrite
15 concentration (micromolar), wherein the ferrite contrast
agent is in aqueous solution with and without a cellulose
polymer (and wherein the cellulose polymer is present with
and without carbon dioxide gas).

DETAILED DESCRIPTION OF INVENTION

20 Any of the wide variety of biocompatible polymers
known in the art may be employed in the medium or methods
of the subject invention. As will be readily apparent to
those skilled in the art, there are numerous types of such
polymers available. Preferably, the polymer chosen is one
25 which has a relatively high water binding capacity. Also
preferably, the polymer has limited ability for ion
complexation. Where imaging of the gastrointestinal region
is desired, preferably the polymer chosen is one which is
not substantially absorbed from or degraded within the
30 gastrointestinal region. The polymers useful in the
present invention can be of either synthetic or natural
origin. As used herein, the term polymer denotes a
compound comprised of two or more repeating monomeric
units, and preferably 10 or more repeating monomeric units.
35 The polymers may be cross-linked, if desired. Preferably,
however, the polymers are not cross-linked.

- 7 -

Exemplary synthetic polymers suitable for use in the present invention include polyethylenes (such as, for example, polyethylene glycol), polyoxyethylenes (such as, for example, polyoxyethylene glycol), polypropylenes (such as, for example, polypropylene glycol), pluronic acids and alcohols, polyvinyls (such as, for example, polyvinyl alcohol), and polyvinyl-pyrrolidone. Exemplary natural polymers suitable for use in the present invention include polysaccharides. Such polysaccharides include, for example, arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan, carrageenan, galactocarlose, pectic acid, amylose, pullulan, glycogen, amylopectin, cellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, dextran, pustulan, chitin, agarose, keratan, chondroitin, dermatan, hyaluronic acid and alginic acid, and various other homopolymers or heteropolymers such as those containing one or more of the following aldoses, ketoses, acids or amines: erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine and neuraminic acid.

Polyethylene glycol (PEG), a polymer that exhibits a high water binding capacity, is particularly preferred for use in the subject invention. As a result of their high water binding capacity and concomitant decrease in the amount of free water in solution, PEG and similar polymers serve to alter the proton density in solution. Furthermore, PEG is used for the fractional precipitation of proteins from solution, which is believed to be due to in part to the excluded volume effects caused by this polymer whereby the protein is excluded from regions of the solution occupied by the polymer and is concentrated up in the water spaces, that is, the extrapolymer spaces, between

- 8 -

the individual molecules of the polymer. This exclusion and concentration effect is illustrated diagrammatically in Figure 1, with the polymer being represented by the squiggly lines and the contrast agent being represented by the solid dots. Since PEG exhibits limited ability for ion complexation, it will also cause a small paramagnetic chelate such as Gd-DTPA to be concentrated such that the effective concentration and the relaxivity of the paramagnetic species will be higher in mixtures with the polymer than in the absence of the polymer. For these and other reasons, PEG, and related polymers, are particularly preferred polymers for the subject invention.

For reasons of diagnostic efficacy, other preferable polymers include polygalacturonic acid and dextran.

The polymers of the present invention may be employed alone, in an aqueous solution, as a contrast medium for magnetic resonance imaging. Alternatively, if desired, the polymers may be employed in admixture with conventional contrast agents. By admixture, it is meant that the contrast agent is simply added to the polymer-containing medium, and is not chemically bound to the polymer by a covalent linkage. Electrostatic interactions or hydrogen bonding may, however, exist between the polymer and contrast agents, and such associations are considered to be within the ambit of the term admixture.

Numerous contrast agents are well known to those skilled in the art and include, for example, paramagnetic, superparamagnetic and proton density contrast agents.

Exemplary paramagnetic contrast agents suitable for use in the subject invention include stable free radicals (such as, for example, stable nitroxides), as well as compounds comprising transition, lanthanide and actinide elements covalently or noncovalently bound to complexing agents or to proteinaceous macromolecules. Preferable elements include Gd(III), Mn(II), Cu(II), Cr(III), Fe(II), Fe(III), Co(II), Er(II), Ni(II), Eu(III) and Dy(III). More

- 9 -

preferably, the elements include Gd(III), Mn(II), Cu(II), Fe(II), Fe(III), Eu(III) and Dy(III), especially Gd(III). Preferable complexing agents include, for example, diethylenetriamine-pentaacetic acid (DTPA), ethylene-
5 diaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-N,N',N',N''-tetraacetic acid (DOTA), 1,4,7,10-tetraazacyclododecane-N,N',N''-triacetic acid (DO3A), 3,6,9-triaza-12-oxa-3,6,9-tricarboxymethylene-10-carboxy-13-phenyl-tridecanoic acid (B-19036),
10 hydroxybenzylethylene-diamine diacetic acid (HBED), N,N'-bis(pyridoxyl-5-phosphate)ethylene diamine, N,N'-diacetate (DPDP), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA) and kryptands (that is, macrocyclic
15 complexes). More preferably, the complexing agents are DTPA, DOTA, DO3A and kryptands, most preferably DTPA. Preferable proteinaceous macromolecules include albumin, collagen, polyarginine, polylysine, polyhistidine, γ -globulin and β -globulin. More preferably, the
20 proteinaceous macromolecules comprise albumin, polyarginine, polylysine, and polyhistidine. Most preferably, the paramagnetic contrast agents employed in the present invention are Gd(III)-DTPA, Gd(III)-DOTA, Gd(III)-DO3A, or Gd(III)-kryptands, especially Gd(III)-
25 DTPA.

Exemplary superparamagnetic contrast agents suitable for use in the subject invention include ferro- or ferrimagnetic compounds, such as pure iron, magnetic iron oxide (such as magnetite), γ -Fe₂O₃, manganese ferrite,
30 cobalt ferrite and nickel ferrite.

Exemplary proton density contrast agents include perfluorocarbons.

The polymer or polymer and contrast agent admixtures of the subject invention may also be employed,
35 if desired, in admixture with biocompatible gases. In the case of both negative and positive contrast agents, such gases often serve to increase the efficacy of the contrast

- 10 -

medium. The gas can be bubbled through the medium using conventional techniques. Any biocompatible gas is suitable for use in the present invention. Numerous such gases are well known to those skilled in the art. Exemplary
5 biocompatible gases include, air, oxygen, carbon dioxide, nitrogen, xenon, neon and argon.

Wide variations in the amounts of the polymer, and the contrast agent and/or gas, can be employed in the contrast medium of the invention. Preferably, however, the
10 polymer is present in a concentration of at least about 1%, by weight, more preferably, between about 5% and about 50%, by weight, and generally most preferably at about 40%, by weight. Of course, as those skilled in the art would recognize, within these parameters the optimum polymer
15 concentration will be influenced by the molecular weight of the polymer, its water binding capacity, as well as other characteristics of the particular polymer employed. Also, preferably, in the case of paramagnetic and proton density contrast agents, the contrast agent is present in a
20 concentration of at least about 0.1 millimolar, more preferably between about 0.5 and about 2 millimolar, most preferably at about 1 millimolar. In the case of superparamagnetic agents, the concentration is preferably at least about 1 micromolar, more preferably between about
25 5 and about 50 micromolar, and most preferably is about 10 micromolar. Where gas is employed, preferably at least about 20 psi is bubbled through the solution for about one minute prior to administration, more preferably between about 30 or about 50 psi, most preferably about 40 psi.

30 The present invention is useful in imaging a patient generally, and/or in specifically diagnosing the presence of diseased tissue in a patient. The imaging process of the present invention may be carried out by administering a contrast medium of the invention to a
35 patient, and then scanning the patient using magnetic resonance imaging to obtain visible images of an internal region of a patient and/or of any diseased tissue in that

- 11 -

region. By region of a patient, it is meant the whole patient or a particular area or portion of the patient. The contrast medium is particularly useful in providing images of the gastrointestinal region, but can also be
5 employed more broadly such as in imaging the vasculature or in other ways as will be readily apparent to those skilled in the art. The phrase gastrointestinal region or gastrointestinal tract, as used herein, includes the region of a patient defined by the esophagus, stomach, small and
10 large intestines and rectum. The phrase vasculature, as used herein, denotes the blood vessels in the body or in an organ or part of the body. The patient can be any type of mammal, but most preferably is a human.

As one skilled in the art would recognize,
15 administration may be carried out in various fashions, such as intravascularly, orally, rectally, etc., using a variety of dosage forms. When the region to be scanned is the gastrointestinal region, administration of the contrast medium of the invention is preferably carried out orally or
20 rectally. The useful dosage to be administered and the particular mode of administration will vary depending upon the age, weight and the particular mammal and region thereof to be scanned, and the particular medium of the invention to be employed. Typically, dosage is initiated
25 at lower levels and increased until the desired contrast enhancement is achieved. Various combinations of biocompatible polymers may be used to modify the relaxation behavior of the medium or to alter properties such as the viscosity, osmolarity or palatability (in the case of
30 orally administered materials). In carrying out the method of the present invention, the contrast medium can be used alone, or in combination with other diagnostic, therapeutic or other agents. Such other agents include excipients such as flavoring or coloring materials. In addition, if
35 desired, the contrast media of the invention may be encapsulated in liposomes or in other delivery vehicles. The polymer or polymer and contrast agent and/or gas

- 12 -

admixture may be sterilized by autoclaving prior to use, if desired.

The magnetic resonance imaging techniques which are employed are conventional and are described, for example, in D.M. Kean and M.A. Smith, Magnetic Resonance Imaging: Principles and Applications, (William and Wilkins, Baltimore 1986). Contemplated MRI techniques include, but are not limited to, nuclear magnetic resonance (NMR) and electronic spin resonance (ESR). The preferred imaging modality is NMR.

As will be apparent to those skilled in the art, the polymer or polymer admixture with contrast agent and/or gas, when employed in magnetic resonance imaging, may operate as a T1, T2 or proton density contrast medium, depending upon the type of polymer used, the molecular weight of the polymer, the concentration of the polymer, the type of contrast agent mixed with the polymer, the type of MRI modality chosen, and the details of the pulse sequence employed for MRI imaging, and all such mechanisms of operation are considered to be within the ambit of the present invention.

The media of the present invention have been shown to be extremely useful as contrast enhancement media in magnetic resonance imaging, particularly in imaging of the gastrointestinal region. By employing the polymers alone or by combining a contrast agent with the polymers in accordance with the present invention, lower overall concentrations of the contrast agents may be used to achieve the same, or in many cases a better degree of, contrast enhancement results. This has benefits not only in terms of toxicity, by avoiding the use of large amounts of the potentially toxic contrast agents, but also in terms of cost, since less of the often more expensive conventional contrast agents are used. Furthermore, in the case of negative contrast agents based on superparamagnetic particles, magnetic susceptibility artifacts will be reduced through the ability to use a lower dose of the

- 13 -

contrast agent. These and other advantages described herein of the present invention will be readily apparent to those skilled in the art, upon reading the present disclosure.

5 The present invention is further described in the following Examples. These Examples are not to be construed with as limiting the scope of the appended Claims.

EXAMPLES

Example 1

10 The polymer polyethylene glycol (PEG), having a molecular weight about 8000, was dissolved in water to various concentrations (w/w; by weight). To some of the aqueous PEG solutions was then added the contrast agent Gd-DTPA, such that the final concentration of Gd-DTPA was 1
15 mM. The relaxivity ($1/T_1$ and $1/T_2$) of the PEG and the PEG and Gd-DTPA solutions was then tested in vitro using a Toshiba MR-50A 0.5 Tesla (T) whole body scanner. The results are shown in Table 1 and Figure 2. As the results indicate, in the presence of PEG the relaxivity of both
20 water and Gd-DTPA is increased.

 At best, it would be expected that the relaxation rates would be simply additive, i.e. the relaxation rate observed would be the sum of the relaxation rates of the individual components. However, an inspection of Table 1
25 and Figure 2 shows that the T_1 relaxation rate of 40% (w/w) PEG 8000 in water was 1.35 ± 0.04 at 0.5 T and the relaxation rate for 1mM Gd-DTPA in water was measured to be 4.68 ± 0.09 at 0.5 T. If the rates were simply additive it would be expected that the observed relaxation rate for 1
30 mM Gd-DTPA in a 40% (w/w) PEG 8000 solution would be approximately $4.68 + 1.35 = 6.03$, at 0.5 T. The results in Table 1 and Figure 2, however, surprisingly reveal that the relaxation rate for the PEG/water/Gd-DTPA mixture was in fact 12.81 ± 0.72 at 0.5 T. In sum, for both T_1 and T_2
35 relaxation rates, it has been observed that the relaxation rate of the polymer/Gd-DTPA admixture is greater than the

- 14 -

sum of the relaxation rates of the PEG solution and the Gd-DTPA solution alone.

The foregoing result is in hindsight believed to arise as a consequence of the exclusion of the Gd-DTPA from the immediate environment of the PEG molecules so that the effective concentration of the Gd-DTPA is increased in the water not bound to the polymer. However, the present invention is not intended to be limited by any theory of operation.

Table 1

Relaxivities at 0.5 T for PEG 8000/Water Mixtures
In the Absence and Presence of 1mM Gd-DTPA

<u>Sample</u>	<u>1/T₁(1/sec)</u>	<u>1/T₂ (1/sec)</u>
water	0.21 ± 0.04	0.65 ± 0.04
15 10% PEG/water	0.41 ± 0.03	0.85 ± 0.03
20% PEG/water	0.64 ± 0.02	1.12 ± 0.06
30% PEG/water	0.96 ± 0.02	1.57 ± 0.05
40% PEG/water	1.35 ± 0.04	2.25 ± 0.08
1mM Gd-DTPA/water	4.68 ± 0.18	5.65 ± 0.03
20 10% PEG/water/1mM Gd-DTPA	5.58 ± 0.23	6.86 ± 0.02
20% PEG/water/1mM Gd-DTPA	7.19 ± 0.53	8.69 ± 0.07
30% PEG/water/1mM Gd-DTPA	9.42 ± 0.58	12.11 ± 0.08
40% PEG/water/1mM Gd-DTPA	12.81 ± 0.72	17.62 ± 0.15

Example 2

Example 1 was substantially repeated, except that the polymer dextrose was employed instead of PEG. The results are shown in Figure 3. As the results indicate, in the presence of dextrose the relaxivity of both water and Gd-DTPA is increased.

As Figure 3 illustrates, again, as with PEG, the relaxivity of the dextrose and Gd-DTPA solution is larger than the sum of the individual relaxation rates.

Example 3

Example 1 was substantially repeated except that an aqueous solution of 1mM Gd-DTPA, 30% (w/w) PEG 8000 and 10% (w/w) dextrose was prepared and T₁ was reported. A T₁

- 15 -

relaxation rate of 11.67 ± 1.09 (1/sec) at 0.5 T was observed.

Examples 1, 2 and 3 show that different polymers or may be used to preferentially alter the T1 or T2 relaxation rates of a solution. For example, as shown in Example 3, a solution of 1mM Gd-DTPA and 30% PEG 8000 and 10% dextrose exhibits a T1 relaxation rate of 11.67 ± 1.09 (1/sec) at 0.5 T. By comparison, 1mM Gd-DTPA and 30% PEG 8000 in solution exhibits a T1 relaxation rate of 9.42 ± 0.58 (1/sec) at 0.5 T, and 1mM Gd-DTPA and 10% dextrose in solution exhibits a T1 relaxation rate of 2.33 ± 0.02 (1/sec) at 0.5 T.

Example 4

Example 1 was substantially repeated, except that 10% (w/w) cellulose, a low toxicity polymer that is not degraded within the gastrointestinal tract, was employed, in aqueous solution with and without different concentrations of a ferrite contrast agent and with and without carbon dioxide gas.

The results are shown in Table 2 and Figure 4. As the results indicate, cellulose is also an efficient T2 relaxation agent, and the T2 relaxivity of cellulose may be improved by mixing with a gas such as carbon dioxide. In addition, the results show that cellulose may be combined with a superparamagnetic contrast agent such as ferrites such that the combined polymer/ferrite contrast agent, whether mixed with gas or not, is superior in terms of relaxivity, as compared with either the polymer or ferrite alone. Specifically, from the results, it can be seen that the T2 relaxivity for a sample containing 10% cellulose with 10mM ferrites after gassification has a higher T2 relaxivity than a 40mM dispersion of ferrites in water. The immediate conclusion is that it would be possible to reduce the dose of ferrites administered by at least a factor of 4 and still obtain the same degree of contrast enhancement. This would have clear benefits in terms of decreasing the potential toxicity of the contrast agent.

- 16 -

Table 2

Relaxivities at 0.5T for water/ferrite
and cellulose/water/ferrite mixtures

<u>Sample</u>	<u>1/T1(1/sec)</u>	<u>1/T2(1/sec)</u>
5 water	0.27 ± 0.05	0.55 ± 0.06
+ 10mM ferrites	1.16 ± 0.01	5.45 ± 0.07
+ 20mM ferrites	1.92 ± 0.03	10.20 ± 0.10
+ 40mM ferrites	3.60 ± 0.10	20.24 ± 0.43
10 % cellulose in water	-	12.76 ± 0.08
10 + pressurized with gas	0.76 ± 0.01	15.95 ± 0.05
gas + 10mM ferrites	1.98 ± 0.03	22.82 ± 0.62
gas + 20mM ferrites	2.41 ± 0.03	26.75 ± 0.32
gas + 40mM ferrites	4.15 ± 0.11	37.42 ± 0.94

15 Example 5

A 2 % aqueous solution of the polymer poly-galacturonic acid in admixture Mn(II) was prepared. The relaxivity (1/T1 and 1/T2) of the solution was then tested in vitro using a Toshiba MRT-50A 0.5 Tesla (T) whole body scanner. The 1/T1 was measured at $41.0 \pm 1.92 \text{ mmol}^{-1}\text{sec}^{-1}$, and the 1/T2 was measured at $79.41 \pm 3.20 \text{ mmol}^{-1}\text{sec}^{-1}$.

Example 6

A 0.5 % aqueous solution of the polymer poly-galacturonic acid was prepared. To the solution was then added 0.1mM Mn (II). The relaxivity (1/T1 and 1/T2) of the solution was tested in vitro using a Toshiba MRT-50A 0.5 Tesla (T) whole body scanner. The 1/T1 was measured at $1.20 \pm 0.056 \text{ sec}^{-1}$, and the 1/T2 was measured at $4.78 \pm 0.001 \text{ sec}^{-1}$.

30 Example 7

The procedures of Example 6 were substantially followed, except that sodium hydroxide was added to the solution in an amount sufficient to raise the pH from 2 (as in Example 6), to a pH of 4, 6, 7, and 8, respectively. The relaxivity (1/T1 and 1/T2) of the solutions at these various pH levels was tested in vitro using a Toshiba MRT-50A 0.5 Tesla (T) whole body scanner. The results are shown below in Table 3.

- 17 -

Table 3

Relaxivities at 0.5T For
Water/Polygalacturonic Acid/Mn (II) Mixtures
At Varying pH Levels

5			
	<u>Sample pH</u>	<u>1/T1(1/sec)</u>	<u>1/T2(1/sec)</u>
	pH 4	4.15 ± 0.208	6.78 ± 0.143
	pH 6	4.10 ± 0.192	7.941 ± 0.320
	pH 7	3.73 ± 0.215	6.29 ± 0.240
10	pH 8	4.11 ± 0.546	6.64 ± 0.268

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall
15 within the scope of the appended Claims.

- 18 -

CLAIMS

What is claimed is:

1. A contrast medium for magnetic resonance imaging comprising an aqueous solution of a biocompatible synthetic polymer in admixture with a contrast agent.
2. A contrast medium of Claim 1 wherein the polymer is selected from the group consisting of polyethylenes polyoxyethylenes, polypropylenes, pluronic acids, pluronic alcohols, polyvinyls, and polyvinylpyrrolidones.
3. A contrast medium of Claim 2 wherein the polymer is a polyethylene which is polyethylene glycol.
4. A contrast medium of Claim 1 wherein the contrast agent is selected from the group consisting of paramagnetic, superparamagnetic, and proton density contrast agents.
5. A contrast medium of Claim 1 wherein the contrast medium further comprises a biocompatible gas.
6. A contrast medium for magnetic resonance imaging comprising an aqueous solution of a biocompatible synthetic non-cross-linked polymer.
7. A contrast medium of Claim 6 wherein the polymer is selected from the group consisting of polyethylenes, polyoxyethylenes, polypropylenes, pluronic acids, pluronic alcohols, polyvinyls, and polyvinylpyrrolidones.
8. A contrast medium of Claim 7 wherein the polymer is a polyethylene which is polyethylene glycol.
9. A contrast medium of Claim 6 wherein the contrast medium further comprises a contrast agent in admixture with the polymer.
10. A contrast medium of Claim 9 wherein the contrast agent is selected from the group consisting of paramagnetic, superparamagnetic, and proton density contrast agents.

- 19 -

11. A contrast medium of Claim 6 wherein the contrast medium further comprises a biocompatible gas.

12. A contrast medium for magnetic resonance imaging consisting essentially of an aqueous solution of at least one biocompatible non-cross-linked polymer.

13. A contrast medium of Claim 12 wherein the polymer is selected from the group consisting of polyethylenes, polyoxyethylenes, polypropylenes, pluronic acids, pluronic alcohols, polyvinyls, and polyvinylpyrrolidones.

14. A contrast medium of Claim 13 wherein the polymer is a polyethylene which is polyethylene glycol.

15. A contrast medium of Claim 12 wherein the non-cross-linker polymer is selected from the group consisting of arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans, levan, fucoidan, carrageenan, galactocarolose, pectic acid, amylose, pullulan, glycogen, amylopectin, cellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, dextran, pustulan, chitin, agarose, keratan, chondroitin, dermatan, hyaluronic acid, alginic acid, and other homopolymers or heteropolymers containing at least one or more aldose, ketose, acid or amine selected from the group consisting of erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine and neuraminic acid.

16. A contrast medium of Claim 15 wherein the non-cross-linked polymer is selected from the group consisting of polygalacturonic acid and dextran.

17. A contrast medium consisting essentially of an aqueous solution of at least one biocompatible polymer and at least one biocompatible gas.

18. A contrast medium of Claim 17 wherein the polymer is selected from the group consisting of

- 20 -

polyethylenes, polyoxyethylenes, polypropylenes, pluronic acids, pluronic alcohols, polyvinyls, and polyvinylpyrrolidones.

19. A contrast medium of Claim 18 wherein the
5 polymer is a polyethylene which is polyethylene glycol.

20. A contrast medium of Claim 17 wherein the polymer is selected from the group consisting of arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans, levan, fucoidan, carrageenan,
10 galactocarolose, pectic acid, amylose, pullulan, glycogen, amylopectin, cellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, dextran, pustulan, chitin, agarose, keratan, chondroitin, dermatan, hyaluronic acid, alginic acid, and other homopolymers or heteropolymers
15 containing at least one or more aldose, ketose, acid or amine selected from the group consisting of erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose,
20 sorbose, tagatose, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic acid, glucosamine, galactosamine and neuraminic acid.

21. A contrast medium of Claim 20 wherein the polymer is selected from the group consisting of
25 polygalacturonic acid and dextran.

22. A contrast medium comprising an aqueous solution of at least one biocompatible polymer selected from the group consisting of polygalacturonic acid and dextran in admixture with a contrast agent.

30 23. A contrast medium of Claim 22 wherein the polymer is polygalacturonic acid.

24. A contrast medium of Claim 22 wherein the contrast agent is a paramagnetic ion which is Mn(II).

25. A method of providing an image of an
35 internal region of a patient comprising (i) administering to the patient a diagnostically effective amount of a contrast medium of Claim 1, and (ii) scanning the patient

- 21 -

using magnetic resonance imaging to obtain visible images of the region.

26. A method for diagnosing the presence of diseased tissue in a patient comprising (i) administering
5 to the patient a diagnostically effective amount of a contrast medium of Claim 1, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images of any diseased tissue in the patient.

27. A method of providing an image of an
10 internal region of a patient comprising (i) administering to the patient a diagnostically effective amount of a contrast medium of Claim 6, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images of the region.

15 28. A method for diagnosing the presence of diseased tissue in a patient comprising (i) administering to the patient a diagnostically effective amount of a contrast medium of Claim 6, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images
20 of any diseased tissue in the patient.

29. A method of providing an image of an internal region of a patient comprising (i) administering to the patient a diagnostically effective amount of a contrast medium of Claim 12, and (ii) scanning the patient
25 using magnetic resonance imaging to obtain visible images of the region.

30. A method for diagnosing the presence of diseased tissue in a patient comprising (i) administering to the patient a diagnostically effective amount of a
30 contrast medium of Claim 12, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images of any diseased tissue in the patient.

31. A method of providing an image of an internal region of a patient comprising (i) administering
35 to the patient a diagnostically effective amount of a contrast medium of Claim 17, and (ii) scanning the patient

- 22 -

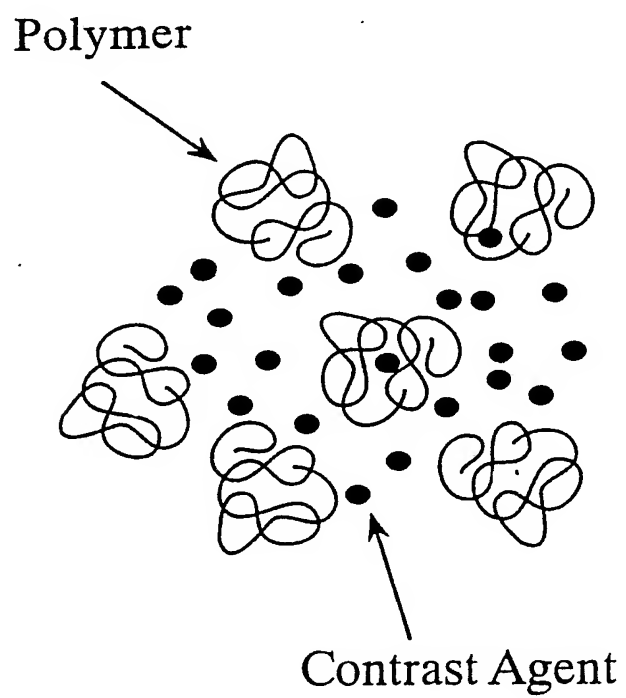
using magnetic resonance imaging to obtain visible images of the region.

32. A method for diagnosing the presence of diseased tissue in a patient comprising (i) administering
5 to the patient a diagnostically effective amount of a contrast medium of Claim 17, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images of any diseased tissue in the patient.

33. A method of providing an image of an
10 internal region of a patient comprising (i) administering to the patient a diagnostically effective amount of a contrast medium of Claim 22, and (ii) scanning the patient using magnetic resonance imaging to obtain visible images of the region.

15 34. A method for diagnosing the presence of diseased tissue in a patient comprising (i) administering to the patient a diagnostically effective amount of a contrast medium of Claim 22, and (ii) scanning the patient
20 using magnetic resonance imaging to obtain visible images of any diseased tissue in the patient.

Figure 1



2/4

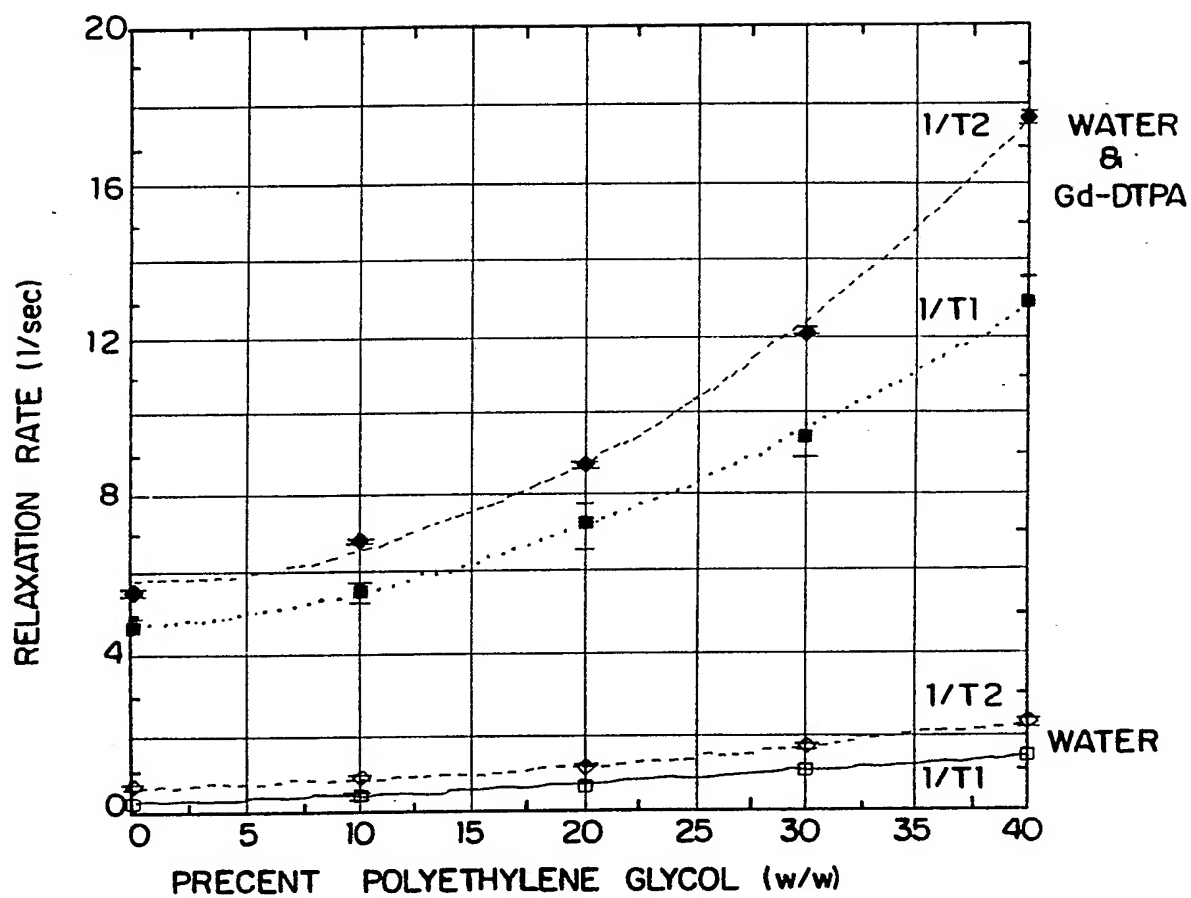


FIG. 2

3/4

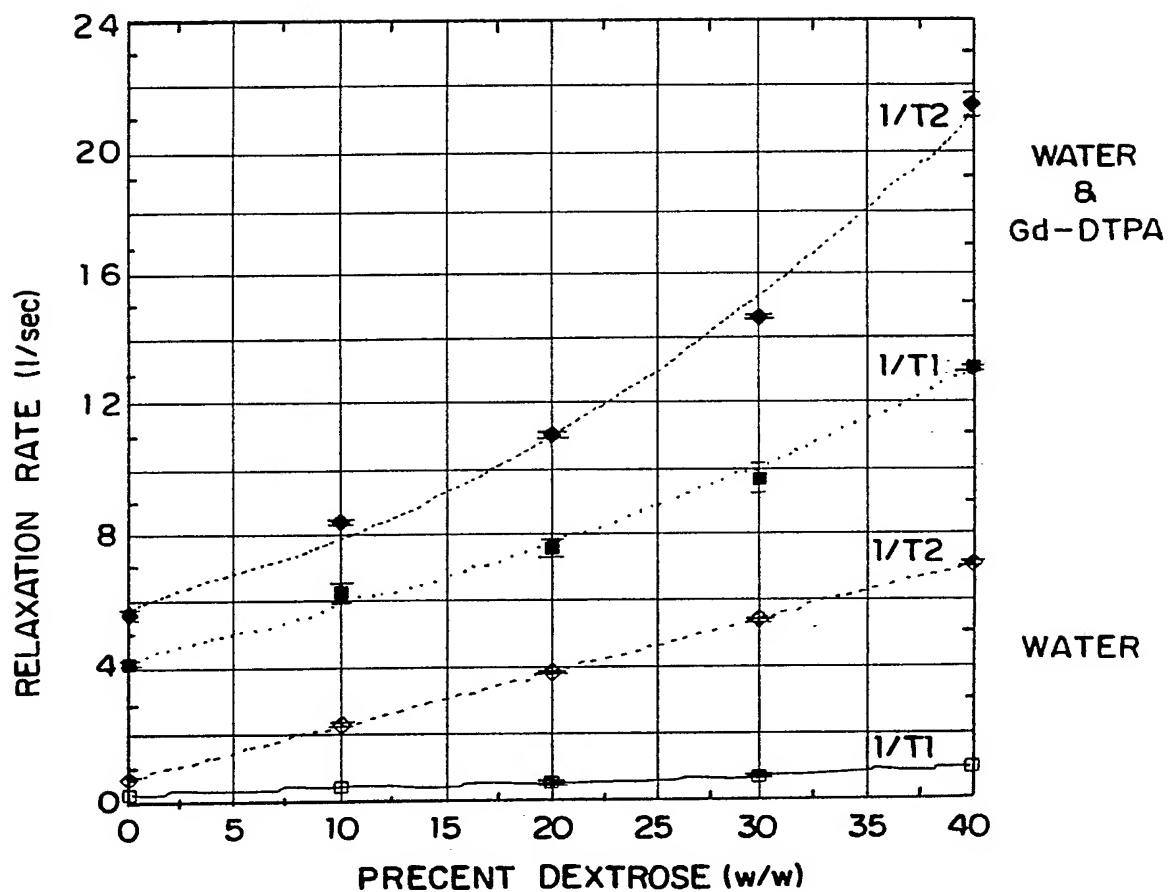
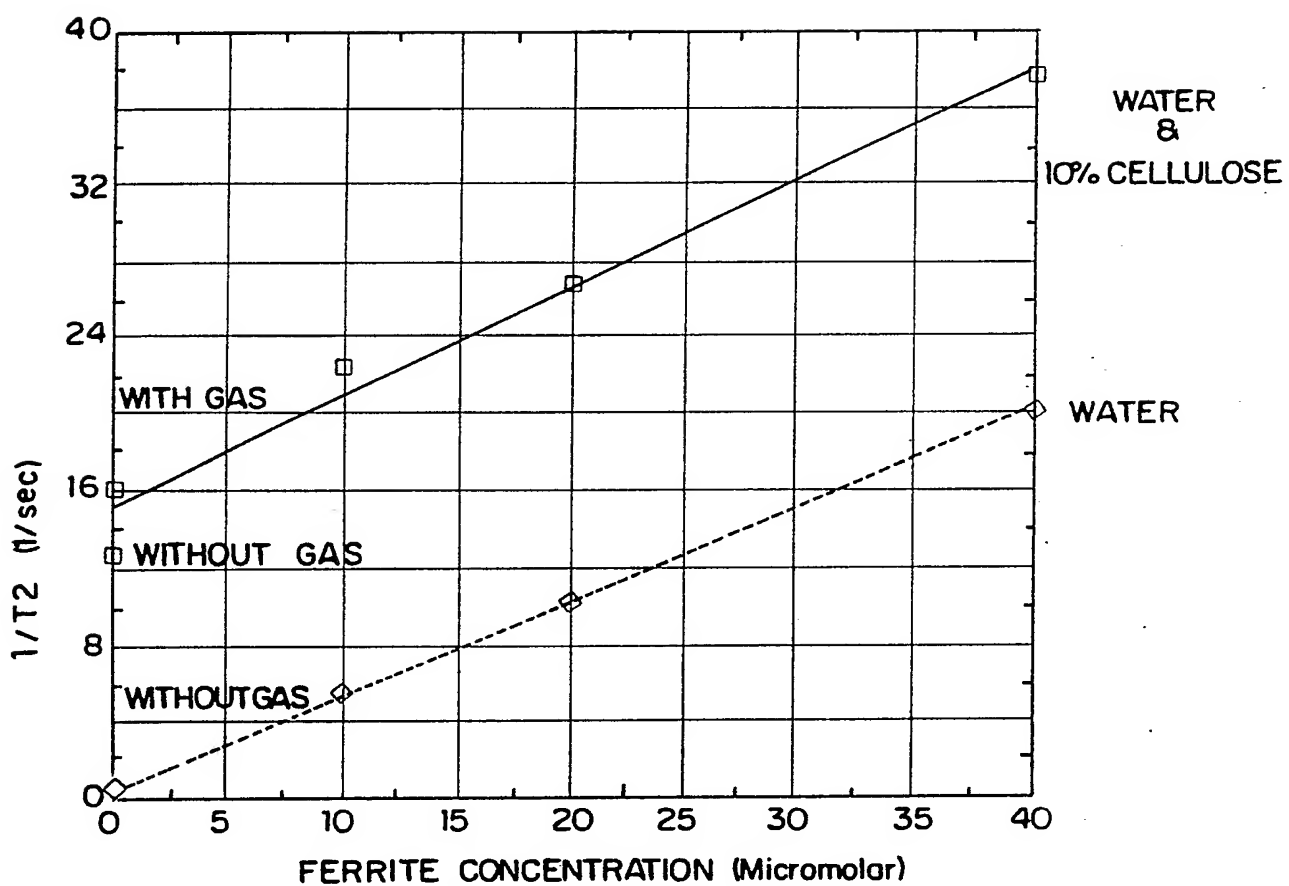


FIG. 3

**FIG. 4**

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/02429

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): G01N 24/00, 31/00 A61B 5/05 A61K 33/40 U.S. Cl: 424/4,9,613 128/653CA 436/173																													
II. FIELDS SEARCHED <div style="text-align: center;">Minimum Documentation Searched ⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%;">Classification System</th> <th style="width: 75%;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; vertical-align: top;">U.S.</td> <td style="text-align: center; vertical-align: top;">424/4,9,613 128/653CA 436/173</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	U.S.	424/4,9,613 128/653CA 436/173																							
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%;">Category [*]</th> <th style="width: 70%;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center;">X</td> <td>US, A, 4,719,098 (Weinmann et al) 12 January 1988 See col.4, line 14 - col.5, line 16</td> <td style="vertical-align: top;">1-4,6-10,12-16, 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US, A, 4,849,210 (Widder) 18 July 1989 See abstract</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">P,X</td> <td>US, A, 4,925,648 (Hansen et al) 15 May 1990 See col.9, lines 3-23</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US, A, 4,729,892 (Beall) 8 March 1988 See col.4, line 5 - col.5, line 3</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US, A, 4,838,274 (Schweighardt et al) 13 June 1989 See col.3, lines 11-36</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US, A, 4,871,716 (Longo et al) 3 October 1989 See col.2, lines 32-40</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">P,X</td> <td>US, A, 4,933,441 (Gibby) 12 June 1990 See col.3, lines 30-38</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> <tr> <td style="text-align: center;">E,X</td> <td>US, A, 4,822,594 (Gibby) 18 April 1989 See abstract</td> <td style="vertical-align: top;">1-4,6-10,12-16 22-30,33,34</td> </tr> </table> <div style="margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> </div>			Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 4,719,098 (Weinmann et al) 12 January 1988 See col.4, line 14 - col.5, line 16	1-4,6-10,12-16, 22-30,33,34	X	US, A, 4,849,210 (Widder) 18 July 1989 See abstract	1-4,6-10,12-16 22-30,33,34	P,X	US, A, 4,925,648 (Hansen et al) 15 May 1990 See col.9, lines 3-23	1-4,6-10,12-16 22-30,33,34	X	US, A, 4,729,892 (Beall) 8 March 1988 See col.4, line 5 - col.5, line 3	1-4,6-10,12-16 22-30,33,34	X	US, A, 4,838,274 (Schweighardt et al) 13 June 1989 See col.3, lines 11-36	1-4,6-10,12-16 22-30,33,34	X	US, A, 4,871,716 (Longo et al) 3 October 1989 See col.2, lines 32-40	1-4,6-10,12-16 22-30,33,34	P,X	US, A, 4,933,441 (Gibby) 12 June 1990 See col.3, lines 30-38	1-4,6-10,12-16 22-30,33,34	E,X	US, A, 4,822,594 (Gibby) 18 April 1989 See abstract	1-4,6-10,12-16 22-30,33,34
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IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; font-size: 1.2em;">16 July 1991</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.5em;">29 JUL 1991</div> </td> </tr> <tr> <td style="width: 50%; padding: 5px;"> International Searching Authority <div style="text-align: center;">ISA/US</div> </td> <td style="width: 50%; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;"> <div style="text-align: center;">Gary E. Hollinden</div> </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; font-size: 1.2em;">16 July 1991</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.5em;">29 JUL 1991</div>	International Searching Authority <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer <div style="text-align: center;"> <div style="text-align: center;">Gary E. Hollinden</div> </div>																							
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	US, A, 4,996,041 (Arai et al) 26 February 1991 See abstract & col.3, lines 34-52	5,11,17-21 31,32
Y	US, A, 4,775,522 (Clark, Jr.) 4 October 1988 See col.11, lines 1-19	5,11,17-21 31,32
Y	US, A, 4,069,306 (Rothman) 17 January 1978	5,11,17-21 31 & 32

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

See attached Telephonic Memo

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Art Unit 129

Continuation of Detailed Reasons for Lack of Unity of Invention

I. Claims 1-3,6-8,12-16, and 25-30, drawn to a contrast medium comprising a polymer and a method of using said polymer for magnetic resonance imaging (MRI), classified in Class 424, subclass 9.

II. Claims 4,9,10,22-24,33, and 34, drawn to drawn to a contrast medium comprising paramagnetic contrast agents, optionally chelated to any of a broad class of chelating agents and a polymer and a method of using said polymer for magnetic resonance imaging (MRI), classified in Class 128, subclass 654CA.

III. Claims 5,11,17-21,21, and 32, drawn to drawn to a contrast medium comprising any biocompatible gas and any polymer and a method of using said polymer for magnetic resonance imaging (MRI), classified in Class 424, subclass 613.

Clearly, a reference which would anticipate Group I would not necessarily anticipate or even make obvious the invention(s) of Groups II-III. Further, the searches of the inventions are not co-extensive, particularly with regard to the literature search required and would constitute an undue burden for the Examiner. One skilled in the art could readily practice the invention of Group I without practicing or infringing the invention(s) of Groups II-III. Since each of the compositions represented above contains such diverse ingredients each is an independant invention and each is capable of supporting its own patent.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.